Azoospermia With Testosterone Therapy Despite Concomitant Intramuscular Human Chorionic Gonadotropin

NYU Case of the Month, July 2018

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A 43-year-old man presented with secondary infertility of 6 months' duration. He had two children from a previous marriage. His current wife was 35 years old and had undergone a reproductive evaluation that was normal. They had been having appropriately timed and unprotected intercourse for 6 months.

Past Medical History

The patient's past medical history was notable for a diagnosis of hypogonadism a year earlier. The patient had complained of fatigue and difficulty recovering from sports injuries. A morning total testosterone level was 250 ng/dL (normal, 30-1100 ng/dL). The patient was started on intramuscular testosterone cypionate, 100 mg weekly. In addition, he was prescribed oral anastrozole, 1 mg, and intramuscular human chorionic gonadotropin (HCG), 500 IU, both twice weekly. The patient had been assured that this regimen would allow for fertility while he was taking exogenous testosterone.

The rest of the patient's medical and surgical history was significant for anxiety and left knee surgery for a torn meniscus. His medications included trazadone and clonazepam. He denied smoking or using illicit drugs and had no relevant family history. He was an investment banker and denied genital trauma or exposure to toxic or radioactive agents.

Evaluation and Management at NYU Langone Health

The patient had a normal masculine hair distribution. His BMI was 27.9. No gynecomastia was present. Testes bilaterally were soft and about 14 cc (normal volume, ≥18 cc). No varicocele was present, and he had a small, benign prostate.

The patient had two semen analyses that were fructose positive with normal volume, normal pH, and no sperm seen on initial analyses. One analysis demonstrated 2 sperm after centrifugation, consistent with cryptozoospermia. Testosterone at baseline was slightly elevated at 1,131 ng/dL and estradiol was undetectable.

The patient was counseled to stop his testosterone injections immediately. He was concerned about becoming symptomatically hypogonadal, as he felt his improved energy levels were important to his work performance. He was started on oral clomiphene citrate (CC), 25 mg, every other day and intramuscular HCG, 3,000 IU, every other day. Three months after starting this regimen, his semen analysis was improved, although he still had oligospermia

at 15×10^6/mL (Table 1). This level remained relatively unchanged at 6 months, at which point his testosterone was in the normal range at 425 ng/dL. By 9 months after therapy initiation, he and his wife had still not conceived naturally. Given the wife's age, the couple underwent a single cycle of intrauterine insemination and she became pregnant. The patient's sperm concentration at the time of intrauterine insemination was 9.4×10^6/mL with 64% motility.

Discussion

Initiating testosterone therapy requires an in-depth discussion with the patient about the risks, benefits, and alternatives. Although certain effects of exogenous testosterone therapy, such as its impact on cardiovascular health, are controversial, the negative impact of exogenous testosterone on spermatogenesis is unequivocal. Intratesticular testosterone, a necessary hormone for spermatogenesis, decreases significantly during exogenous testosterone therapy. In fact, exogenous testosterone was investigated as a male contraceptive agent, and it was found to result in azoospermia in approximately 75% of men after only 6 months of use.[1] For this reason, the 2018 guidelines of both the Endocrine Society and the American Urological Association recommend against testosterone therapy in men wishing to preserve fertility.[2,3]

Only a single retrospective case series exists to support the use of HCG to preserve fertility while taking testosterone.[4] The authors described the use of HCG, 500 IU, every other day in 26 hypogonadal men initiating exogenous testosterone therapy. Three quarters of the men were treated with intramuscular testosterone, and the remainder used topical gel. Semen analysis parameters remained unchanged after an average of 6 months' follow-up and no man experienced azoospermia. Although these data are intriguing, caution should be exercised in applying this regimen to men interested in fertility, as the current case makes clear.

One management option for men who present with azoospermia associated with testosterone therapy is simply cessation of the therapy. In an integrated analysis of 1549 men in various male hormonal contraceptive studies, the median time to recover to a sperm concentration of 20 million/mL was 3.4 months and median time to recover to baseline sperm concentration was 5.4 months.[5] Ninety percent of men recovered to 20 million/mL by 12 months, and 100% recovered by 24 months. Of note, these were relatively young men (average age, 31.8 years), all of whom had a baseline sperm concentration of at least 20 million/mL, and they were treated with androgens for an average of only 9.5 months.

Concerns about female age often play an important role in shared decision making with couples facing infertility. Thus, the prospect of shortening the time to recovery of spermatogenesis is appealing, and many couples prefer a more active approach to managing the recovery of spermatogenesis after testosterone therapy. Various protocols have been described to treat infertility due to testosterone therapy. We use concomitant CC and HCG. HCG is structurally like luteinizing hormone and thus induces the testicular Leydig cells to produce testosterone (Figure 1). CC is a selective estrogen

TABLE 1

Hormone and Semen Analysis Parameters During Treatment

Parameter	Baseline	3 Months	6 Months	Reference Range
Semen volume	4.6 mL	4.8 mL	4.5 mL	≥2 mL
Semen pH	8.3	8.2	8.3	≥7.2
Sperm concentration	0	15×10^6/mL	14×10^6/mL	$\geq 20 \times 10^6$/mL
Sperm motility		66%	82%	≥50%
Sperm morphology		20%	18%	≥14%
Total testosterone	1,131 ng/dL		425 ng/dL	300–1100 ng/dL
Estradiol	<5.0 pg/mL		12.9 pg/mL	7.6–42.6 pg/mL
Medications	Testosterone HCG Anastrozole	Clomiphene HCG	Clomiphene HCG	

HCG, human chorionic gonadotropin.

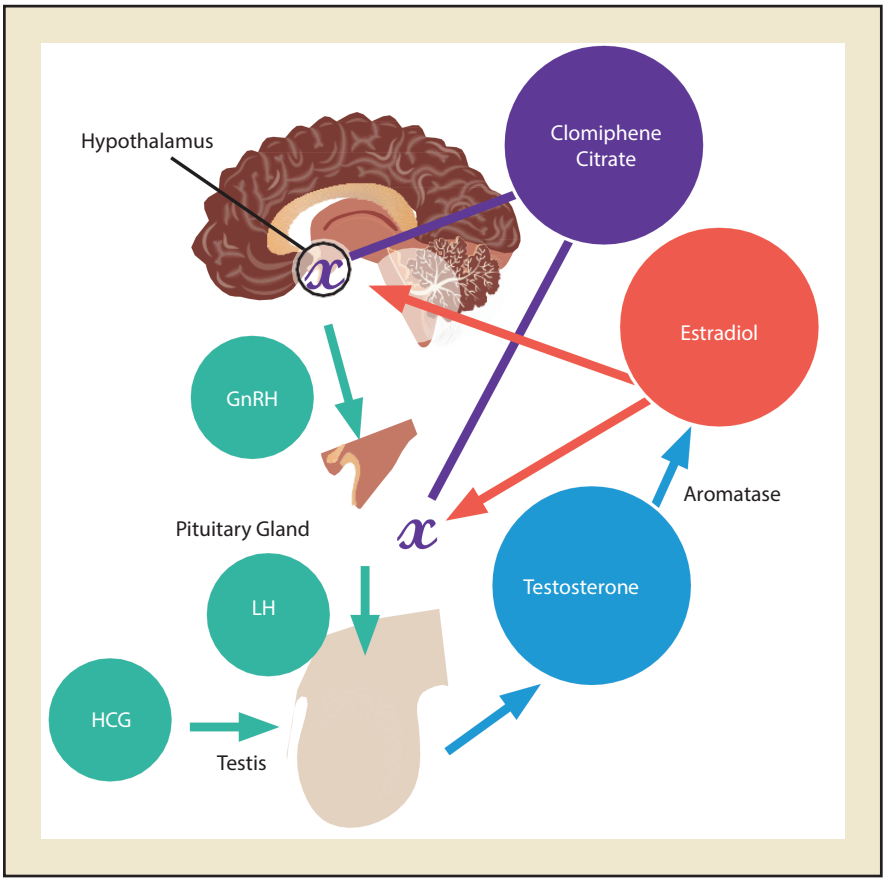

Figure 1. Clomiphene citrate is a selective estrogen receptor modulator that competitively binds the estrogen receptor in the hypothalamus and the pituitary gland. HCG is structurally like LH. GnRH, gonadotropin-releasing hormone; HCG, human chorionic gonadotropin; LH, luteinizing hormone.

receptor modulator that competitively binds to the estrogen receptor in the hypothalamus and the pituitary gland. This interaction decreases the negative feedback of estradiol and results in an increase in gonadotropin-releasing hormone, luteinizing hormone, and follicle-stimulating hormone. The goal of this protocol is to shorten time to fertility by providing stronger testicular stimulation for sperm production.

Concomitant use of CC and HCG is supported by a series of 66 men with either azoospermia or cryptozoospermia due to exogenous testosterone use for an average of 2 years.[6] Seventy percent of these men achieved a total motile sperm count of at least 5 million within a year of stopping exogenous testosterone and starting CC and HCG. This endpoint was used because it is a reasonable threshold for determining whether intrauterine insemination can be used instead of in vitro fertilization. Older age and longer duration of exogenous testosterone therapy were negative predictors of recovery. Of the 18% of men with cryptozoospermia at baseline, 91.7% recovered sperm production to this degree, whereas only 64.8% of men with azoospermia experienced a similar recovery. Unfortunately, there are no controlled trials comparing the CC and HCG protocol with testosterone cessation alone.

This patient had initiated testosterone therapy a year before presentation at NYU Langone, and he was taking HCG at the same dose and frequency as reported in the case series of 26 men with preserved fertility.[4] Despite this, he experienced azoospermia. The average duration of concomitant HCG and testosterone therapy in that study was only 6 months, so perhaps this patient's longer duration of testosterone therapy played a role in his different outcome. Furthermore, unlike the men in that study, this patient did not undergo a baseline semen analysis. Although his sperm concentration increased by 3 months, it appeared to have stabilized in the low range. Even though all men in the testosterone contraceptive trials had a normal baseline semen analysis, men with lower sperm concentrations were slower to recover.[5] It's likely that this patient has some degree of testicular dysfunction that resulted in azoospermia despite his being on concomitant HCG and testosterone. A baseline semen analysis prior to initiating therapy is advisable to identify such patients.

Multiple organizational guidelines recommend against exogenous testosterone therapy in men interested in fertility. Evidence supporting fertility preservation with concomitant HCG and testosterone is limited, and given this patient's experience, caution should be exercised in recommending this protocol to men desiring fertility. CC and HCG can be helpful for restoring spermatogenesis in these men, after cessation of testosterone therapy. ■

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